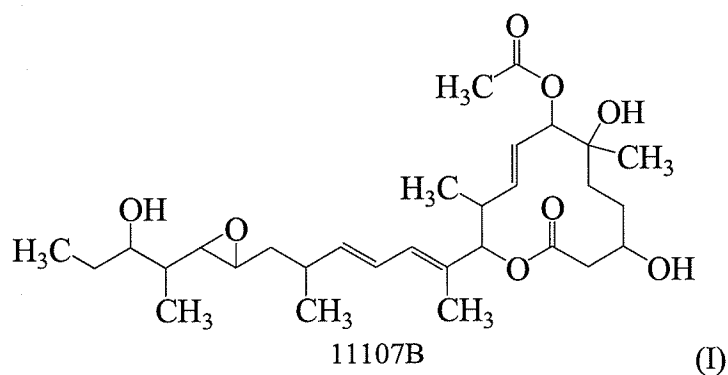
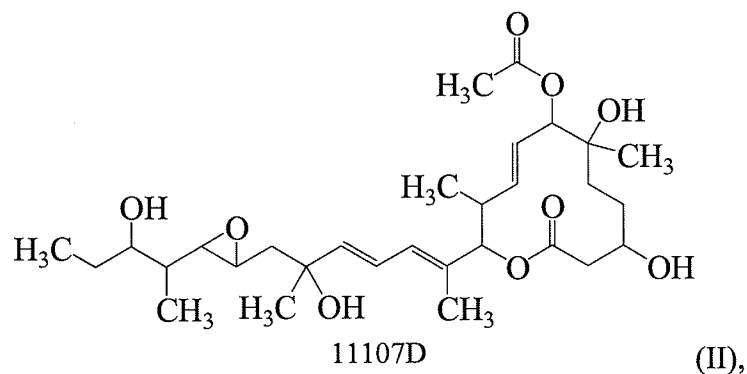


### AMENDMENTS TO THE CLAIMS

1. (Currently Amended) A DNA participating in biological transformation of a macrolide compound (hereinafter referred to as a macrolide compound 11107B) represented by the formula (I):



into a 16-position hydroxy macrolide compound represented by the formula (II):



the DNA being an isolated and pure DNA comprising a DNA encoding a protein having 16-position hydroxylating enzymatic activity ~~or ferredoxin, partly or entirely or its variant~~ which is characterized by the following (a), (b), or (c):

(a) a DNA encoding a protein having the enzymatic activity to hydroxylate the 16-position of the macrolide compound 11107B, wherein the DNA is selected from the group consisting of (1) a continuous nucleotide sequence from base 1322 to base 2548 of SEQ ID NO: 1; (2) a continuous nucleotide sequence from base 420 to base 1604 of SEQ ID NO: 2; and a continuous nucleotide sequence from base 172 to base 1383 of SEQ ID NO: 3;

(b) a DNA which has a nucleotide sequence having 90% or more identity with the DNA described in (a);

(c) a DNA encoding a protein having the same amino acid sequence as the protein encoded by the DNA described in (a) or (b) though it does not have 90% or more identity with the DNA described in (a) because of the degeneracy of a gene codon.

2. (Canceled)

3. (Withdrawn, Currently Amended) A protein encoded by the DNA as claimed in Claim [[2]] 1.

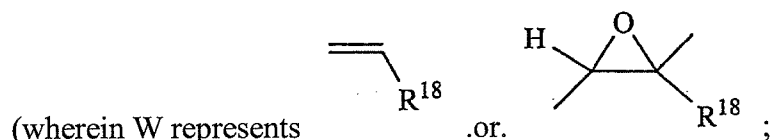
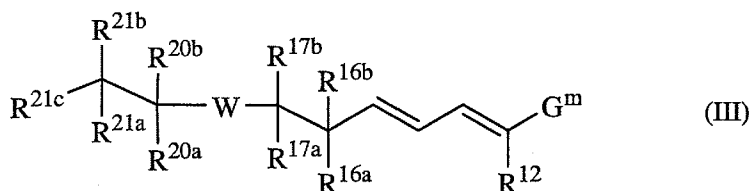
4. (Currently Amended) A self-replicative or integrating replicative recombinant plasmid carrying the DNA as claimed in Claim 1 [[2]].

5. (Original) A transformant into which the recombinant plasmid as claimed in Claim 4 transforms.

6. (Withdrawn, Currently Amended) A method of isolating a DNA encoding a protein having enzymatic activity in hydroxylating the 16-position of the macrolide compound 11107B, the method characterized by using the DNA as claimed in Claim [[2]] 1 or a DNA constituted of a part of the DNA as a probe or a primer.

7-11. (Canceled)

12. (Withdrawn, Currently Amended) A method of producing a 16-position hydroxy macrolide compound, the method comprises the steps of culturing the transformant as claimed in Claim 5 or 10 in a medium; bringing the proliferated transformant into contact with a macrolide compound represented by the formula (III):



$R^{12}$ ,  $R^{16b}$ ,  $R^{17a}$ ,  $R^{17b}$ ,  $R^{18}$ ,  $R^{20a}$ ,  $R^{20b}$ ,  $R^{21a}$  and  $R^{21b}$ , which may be the same as or different from, respectively represent:

- (1) hydrogen atom;
- (2) a  $C_{1-22}$  alkyl group which may have a substituent;
- (3) -OR (wherein R represents:
  - 1) hydrogen atom; or
  - 2) a  $C_{1-22}$  alkyl group;
  - 3) a  $C_{7-22}$  aralkyl group;
  - 4) a 5-membered to 14-membered heteroaryloxyalkyl group;
  - 5) a  $C_{2-22}$  alkanoyl group;
  - 6) a  $C_{7-15}$  aroyl group;
  - 7) a  $C_{3-23}$  unsaturated alkanoyl group;

8)  $-\text{COR}^{\text{co}}$  (wherein  $\text{R}^{\text{co}}$  represents:

8-1) a 5-membered to 14-membered heteroaryloxyaryl group;

8-2) a  $\text{C}_{1-22}$  alkoxy group;

8-3) an unsaturated  $\text{C}_{2-22}$  alkoxy group;

8-4) a  $\text{C}_{6-14}$  aryloxy group;

8-5) a 5-membered to 14-membered heteroaryloxy group; or

8-6) a 3-membered to 14-membered nitrogen-containing non-aromatic heterocyclic group, each of which may have a substituent);

9) a  $\text{C}_{1-22}$  alkylsulfonyl group;

10) a  $\text{C}_{6-14}$  arylsulfonyl group; or

11)  $-\text{SiR}^{\text{s1}}\text{R}^{\text{s2}}\text{R}^{\text{s3}}$ , (wherein  $\text{R}^{\text{s1}}$ ,  $\text{R}^{\text{s2}}$  and  $\text{R}^{\text{s3}}$ , which may be the same as or different from, respectively represent a  $\text{C}_{1-6}$  alkyl group or a  $\text{C}_{6-14}$  aryl group), each of which may have a substituent);

(4) a halogen atom; or

(5)  $-\text{R}^{\text{M}}-\text{NR}^{\text{N1}}\text{R}^{\text{N2}}$ , {wherein  $\text{R}^{\text{M}}$  represents a single bond or  $-\text{O}-\text{CO}-$ ; and  $\text{R}^{\text{N1}}$  and  $\text{R}^{\text{N2}}$

1) may be the same as or different from, respectively represent:

1-1) hydrogen atom; or

1-2)

(i) a  $\text{C}_{1-22}$  alkyl group;

(ii) an unsaturated  $\text{C}_{2-22}$  alkyl group;

(iii) a  $\text{C}_{2-22}$  alkanoyl group;

(iv) a  $\text{C}_{7-15}$  aroyl group;

- (v) an unsaturated C<sub>3-23</sub> alkanoyl group;
- (vi) a C<sub>6-14</sub> aryl group;
- (vii) a 5-membered to 14-membered heteroaryl group;
- (viii) a C<sub>7-22</sub> aralkyl group;
- (ix) a C<sub>1-22</sub> alkylsulfonyl group; or
- (x) a C<sub>6-14</sub> arylsulfonyl group, each of which may have a substituent, or

2) and R<sup>N1</sup> and R<sup>N2</sup> may be combined with the nitrogen atom to which they bound, to form a 3-membered to 14-membered nitrogen-containing non-aromatic heterocyclic group}, provided that

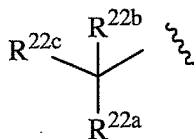
R<sup>21a</sup> and R<sup>21b</sup> may be combined with each other to form (i) a ketone structure (=O) or (ii) an oxime structure {=NOR<sup>ox</sup> (wherein R<sup>ox</sup> represents a C<sub>1-22</sub> alkyl group, an unsaturated C<sub>2-22</sub> alkyl group, a C<sub>6-14</sub> aryl group, a 5-membered to 14-membered heteroaryl group or a C<sub>7-22</sub> aralkyl group, each of which may have a substituent)};

R<sup>16a</sup> represents hydrogen atom;

R<sup>21c</sup> represents:

(1) hydrogen atom; or

(2)



(wherein R<sup>22a</sup>, R<sup>22b</sup> and R<sup>22c</sup>, which may be the same as or different from, respectively represent:

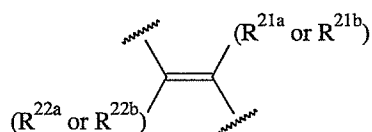
- 1) hydrogen atom;
- 2) a C<sub>1-6</sub> alkyl group;

3) -OR (wherein R has the same meaning as the above);

4)  $-R^M-NR^{N1}R^{N2}$  (wherein  $R^M$ ,  $R^{N1}$  and  $R^{N2}$  have the same meanings as the above); or

5) a halogen atom, or

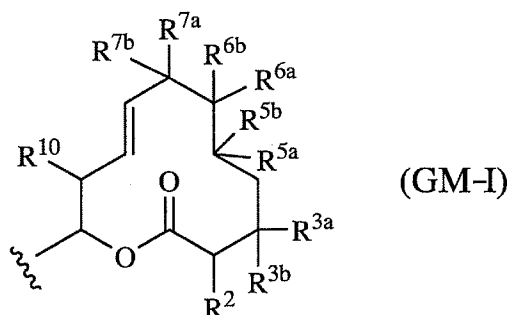
any one of  $R^{21a}$  and  $R^{21b}$  may be combined with any one of  $R^{22a}$  and  $R^{22b}$  to form the partial structure;



); and

$G^m$  represents:

(1) a group represented by the formula (GM-I):



{wherein

$R^2$  and  $R^{10}$ , which may be the same as or different from , respectively represent hydrogen atom or a  $C_{1-22}$  alkyl group;

$R^{3a}$ ,  $R^{3b}$ ,  $R^{5a}$ ,  $R^{5b}$ ,  $R^{6a}$  and  $R^{6b}$ , which may be the same as or different from, respectively represent:

1) hydrogen atom;

2) hydroxyl group;

3)

3-1) a C<sub>1-22</sub> alkyl group;

3-2) a C<sub>1-22</sub> alkoxy group;

3-3) a C<sub>6-14</sub> aryloxy group;

3-4) a 5-membered to 14-membered heteroaryloxy group;

3-5) a C<sub>2-22</sub> alkanoyloxy group;

3-6) a C<sub>7-15</sub> aroyloxy group;

3-7) a C<sub>3-23</sub> unsaturated alkanoyloxy group;

3-8) -OCOR<sup>co</sup> (wherein R<sup>co</sup> has the same meaning as the above);

3-9) a C<sub>1-22</sub> alkylsulfonyloxy group;

3-10) a C<sub>6-14</sub> arylsulfonyloxy group; or

3-11) -OSiR<sup>s1</sup>R<sup>s2</sup>R<sup>s3</sup> (wherein R<sup>s1</sup>, R<sup>s2</sup> and R<sup>s3</sup> have the same meanings as the above),

each of which may have a substituent;

4) a halogen atom; or

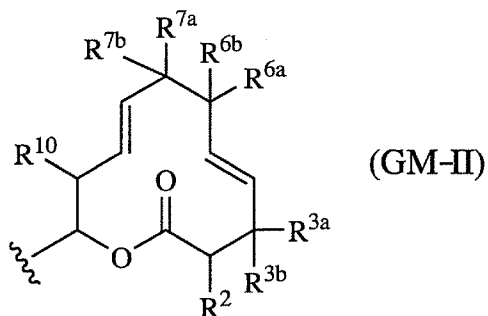
5) -R<sup>M</sup>-NR<sup>N1</sup>R<sup>N2</sup> (wherein R<sup>M</sup>, R<sup>N1</sup> and R<sup>N2</sup> have the same meanings as the above); or

R<sup>5a</sup> and R<sup>5b</sup> may be combined with each other to form a ketone structure (=O); or

R<sup>6a</sup> and R<sup>6b</sup> may be combined with each other to form a spirooxysilanyl group or an exomethylene group; or

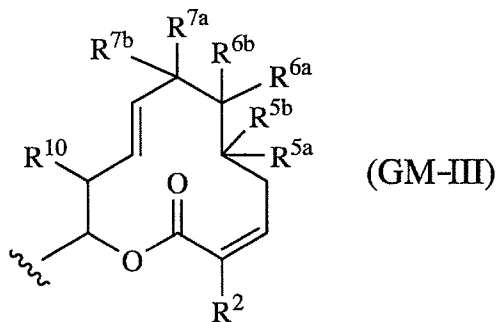
R<sup>7a</sup> and R<sup>7b</sup>, which may be the same as or different from, respectively represent hydrogen atom or -OR<sup>H</sup> (wherein R<sup>H</sup> represents hydrogen atom, a C<sub>1-22</sub> alkyl group or a C<sub>2-22</sub> alkanoyl group));

(2) a group represented by the formula (GM-II):



(wherein  $R^2$ ,  $R^{3a}$ ,  $R^{3b}$ ,  $R^{6a}$ ,  $R^{6b}$ ,  $R^{7a}$ ,  $R^{7b}$  and  $R^{10}$  have the same meanings as those in the formula (GM-I));

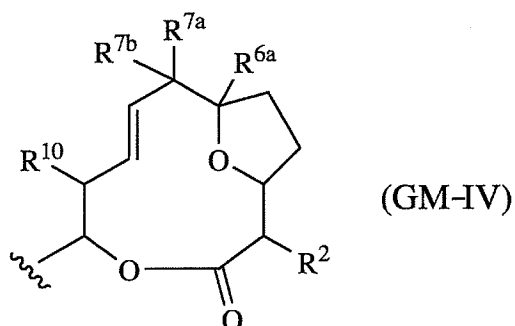
(3) a group represented by the formula (GM-III):



(wherein  $R^2$ ,  $R^{5a}$ ,  $R^{5b}$ ,  $R^{6a}$ ,  $R^{6b}$ ,  $R^{7a}$ ,  $R^{7b}$  and  $R^{10}$  have the same meanings as those in the formula (GM-I));

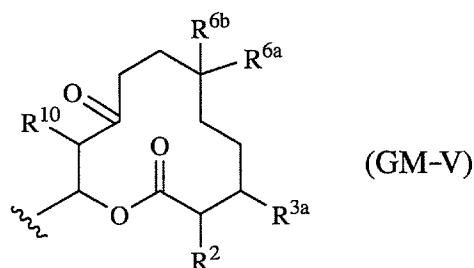
(4) a group represented by the formula (GM-IV):





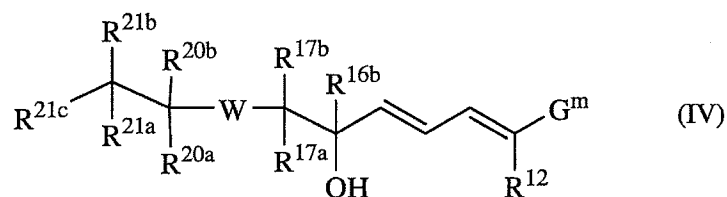
(wherein  $R^2$ ,  $R^{6a}$ ,  $R^{7a}$ ,  $R^{7b}$  and  $R^{10}$  have the same meanings as those in the formula (GM-I)); or

(5) a group represented by the formula (GM-V):



(wherein  $R^2$ ,  $R^{3a}$ ,  $R^{6a}$ ,  $R^{6b}$  and  $R^{10}$  have the same meanings as those in the formula (GM-I))

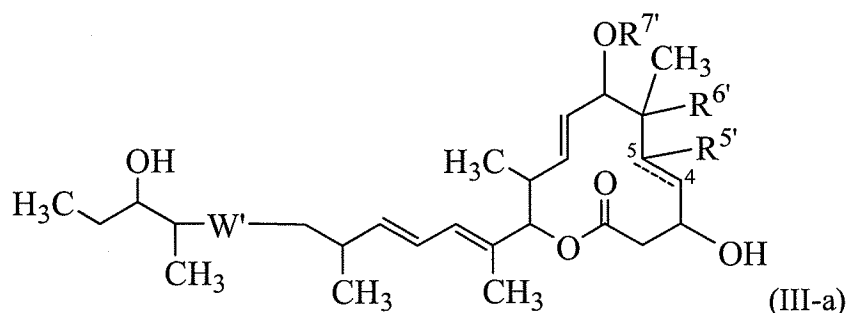
during or after culturing, to convert it into a 16-position hydroxy macrolide compound represented by the formula (IV):



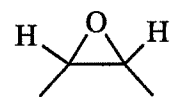
(wherein  $W$ ,  $R^{12}$ ,  $R^{16b}$ ,  $R^{17a}$ ,  $R^{17b}$ ,  $R^{20a}$ ,  $R^{20b}$ ,  $R^{21a}$ ,  $R^{21b}$ ,  $R^{21c}$  and  $G^m$  have the same meanings as those in the formula (III)); and then collecting the 16-position hydroxy macrolide compound thus converted.

13. (Canceled)

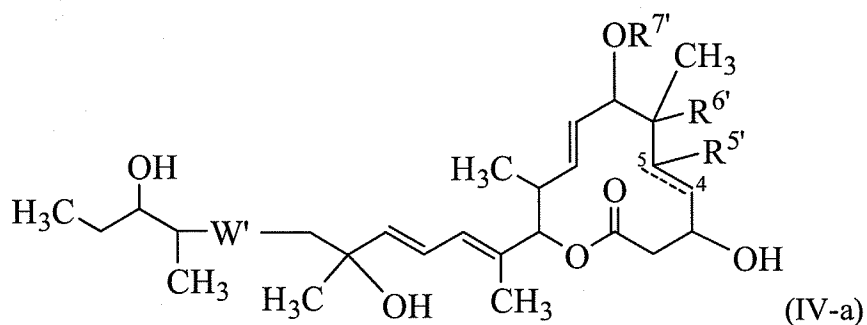
14. (Withdrawn) The production method according to Claim 12, the method comprises the step of converting a compound represented by the formula (III-a):



(wherein  $5 \text{---} 4$  represents a double bond or a single bond;  $W'$  represents a double bond or

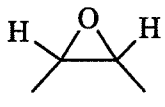


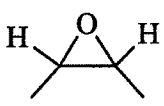
;  $R^{5'}$  represents hydrogen atom or an acetoxy group;  $R^{6'}$  represents hydrogen atom or hydroxyl group; and  $R^{7'}$  represents hydrogen atom or acetyl group) into a compound represented by the formula (IV-a):

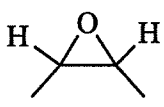


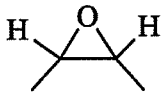
(wherein  $5 \equiv 4$ ,  $W'$ ,  $R^{5'}$ ,  $R^{6'}$  and  $R^{7'}$  have the same meanings as those in the formula (III-a)).

15. (Withdrawn) The production method according to Claim 14, wherein, in the conversion of the compound of the formula (III-a) into the compound of the formula (IV-a), the compound to be subjected is a compound selected from the group consisting of:

(1) a compound in which  $5 \equiv 4$  is a single bond;  $W'$  is ; and  $R^{5'}$ ,  $R^{6'}$  and  $R^{7'}$  are respectively hydrogen atom;

(2) a compound in which  $5 \equiv 4$  is a single bond,  $W'$  is ;  $R^{5'}$  and  $R^{6'}$  are respectively hydrogen atom; and  $R^{7'}$  is acetyl group;

(3) a compound in which  $5 \equiv 4$  is a single bond,  $W'$  is ;  $R^{5'}$  and  $R^{7'}$  are respectively hydrogen atom; and  $R^{6'}$  is hydroxyl group;

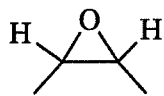
(4) a compound in which  $5 \equiv 4$  is a single bond, W' is ; R<sup>5'</sup> is hydrogen atom, R<sup>6'</sup> is hydroxy group; and R<sup>7'</sup> is acetyl group;

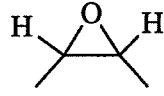
(5) a compound in which  $5 \equiv 4$  is a single bond; W' is a double bond; and R<sup>5'</sup>, R<sup>6'</sup> and R<sup>7'</sup> are respectively hydrogen atom;

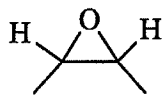
(6) a compound in which  $5 \equiv 4$  is a single bond; W' is a double bond; R<sup>5'</sup> and R<sup>6'</sup> are respectively hydrogen atom; and R<sup>7'</sup> is acetyl group;

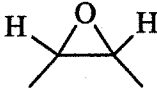
(7) a compound in which  $5 \equiv 4$  is a single bond; W' is a double bond; R<sup>5'</sup> and R<sup>7'</sup> are respectively hydrogen atom; and R<sup>6'</sup> is hydroxyl group;

(8) a compound in which  $5 \equiv 4$  is a single bond; W' is a double bond; R<sup>5'</sup> is hydrogen atom; R<sup>6'</sup> is hydroxy group; and R<sup>7'</sup> is acetyl group;

(9) a compound in which  $5 \equiv 4$  is a double bond; W' is ; R<sup>5'</sup> and R<sup>7'</sup> are respectively hydrogen atom; and R<sup>6'</sup> is hydroxyl group;

(10) a compound in which  $5 \equiv 4$  is a double bond; W' is ; R<sup>5'</sup> is hydrogen atom; R<sup>6'</sup> is hydroxy group; and R<sup>7'</sup> is acetyl group;

(11) a compound in which  $5 \equiv 4$  is a single bond; W' is ; R<sup>5'</sup> is acetoxo group; R<sup>6'</sup> is hydroxyl group; and R<sup>7'</sup> is hydrogen atom; and

(12) a compound in which  $5 \equiv 4$  is a single bond; W' is ; R<sup>5'</sup> is an acetoxy group; R<sup>6'</sup> is hydroxyl group; and R<sup>7'</sup> is acetyl group.

16. (Withdrawn, Currently Amended) Use of the transformant as claimed in Claim 5 or 10 for producing a 16-position hydroxy macrolide compound.

17. (New) The DNA according to claim 1, wherein the DNA comprises bases 1322-2548 of SEQ ID NO: 1.

18. (New) The DNA according to claim 1, wherein the DNA encodes a polypeptide comprising amino acids 1-409 of SEQ ID NO: 1.

19. (New) The DNA according to claim 1, wherein the DNA consists of bases 1322-2548 of SEQ ID NO: 1.

20. (New) The DNA according to claim 1, wherein the DNA encodes a polypeptide consisting of amino acids 1-409 of SEQ ID NO: 1.

21. (New) The DNA according to claim 1, wherein said identity in (b) and (c) of claim 1 is 95% or more.

22. (New) A DNA comprising

(a) a DNA encoding a protein, wherein the DNA is selected from the group consisting of (1) a continuous nucleotide sequence from base 1322 to base 2548 of SEQ ID NO: 1; (2) a continuous nucleotide sequence from base 420 to base 1604 of SEQ ID NO: 2; and a continuous nucleotide sequence from base 172 to base 1383 of SEQ ID NO: 3;

(b) a DNA which has a nucleotide sequence having 90% or more identity with the DNA described in (a); or

(c) a DNA encoding a protein having the same amino acid sequence as the protein encoded by the DNA described in (a) or (b) though it does not have 90% or more identity with the DNA described in (a) because of the degeneracy of a gene codon.

23. (New) The DNA according to claim 22, wherein said identity in (b) and (c) of claim 22 is 95% or more.

24. (New) The DNA according to claim 1, wherein the DNA comprises bases 420-1604 of SEQ ID NO: 2.

25. (New) The DNA according to claim 1, wherein the DNA encodes a polypeptide comprising amino acids 1-395 of SEQ ID NO: 2.

26. (New) The DNA according to claim 1, wherein the DNA consists of bases 420-1604 of SEQ ID NO: 2.

27. (New) The DNA according to claim 1, wherein the DNA encodes a polypeptide consisting of amino acids 1-395 of SEQ ID NO: 2.

28. (New) The DNA according to claim 1, wherein the DNA comprises bases 172-1383 of SEQ ID NO: 3.

29. (New) The DNA according to claim 1, wherein the DNA encodes a polypeptide comprising amino acids 1-404 of SEQ ID NO: 3.

30. (New) The DNA according to claim 1, wherein the DNA consists of bases 172-1383 of SEQ ID NO: 3.

31. (New) The DNA according to claim 1, wherein the DNA encodes a polypeptide consisting of amino acids 1-404 of SEQ ID NO: 3.